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MERCHANT GOULD SMITH EDELL
WELTER & SCHMIDT
3100 NORWEST CENTER
90 SOUTH SEVENTH STREET
MINNEAPOLIS MN 55402-4131

EXAMINER	
CONNELL, Y	
ART UNIT	**PAPER NUMBER**
1632	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

Application No.	Applicant(s)
09/254,529	Susan M. Kingsman et al.
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-16 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-16 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C.371 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). Applicant must state specifically: This is the National Stage of International Application No. PCT/GB97/02859, filed 10/17/97.

Claim Rejections - 35 U.S.C. § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15 and 16 are rejected under 35 U.S.C.101 since the claimed invention is directed to non-statutory subject matter. The terminology used in these claims for target cells transduced or infected by a retroviral vector for use in gene therapy, encompasses cells as implanted in a human or in a human who has been made transgenic by the presence of such constructs, as well as the human thereof. Claims directed to or including within its scope a human, will not be considered patentable subject matter under 35 U.S.C. 101. The grant of a limited, but exclusive property right of a human being is prohibited by the Constitution. See 1077 OG 24.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,13, and 15 are rejected under 35 U.S.C. 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 1 and 13 are rejected for use of the language "capable of". The term "capable of" implies some conditional function which is merely a recitation of a latent characteristic, the scope of which is unclear.

Claim 15 provides for the "use of a retroviral vector", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 15 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 16 is rejected for use of the language "target cells". The grammar between independent and dependent claims is incorrect, because the claim lacks a preceding article for the preamble. The definite article "The" should be used at the beginning of the preamble since the recited claim is dependent upon the preceding claim 15.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 16 are rejected under 35 U.S.C. 112 first paragraph, because the specification while being enabling for a retroviral particle such as the TIN or TRIN vectors, comprising a packagable RNA genome capable of being inserted into a target cell genome in the form of a DNA provirus, having an expressible gene of interest, the RevM10 gene, to be located within an intron in a transcription unit of the provirus and, where the transcription unit further comprises a polynucleotide response element responsive such as Rev and RRE, to a nucleus to cytoplasm factor, does not reasonably provide enablement for the use of any retroviral vector comprising an RNA genome encoding any therapeutic gene located in any intron within the transcription unit of the provirus, comprising any polynucleotide response element responsive to a nucleus to cytoplasm transport, for the infection or transduction of any target cell in gene therapy for the treatment or prevention of retrovirus infections such as HIV. The specification does not enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

1. Claimed invention. The claims are drawn to a retroviral vector particle comprising a packagable RNA genome capable of being inserted and expressed in a target cell genome, when in the form of a DNA provirus. The RNA genome encodes at least one selected gene, located within an intron in a transcription unit of the provirus, where the transcription unit further

comprises a polynucleotide response element responsive to a nucleus to cytoplasm transport. The claimed invention is drawn to a method of using the above delineated retroviral particle for gene therapy for the treatment or prevention of retroviral infections such as HIV.

2. The *in vitro* examples and results on pages 21-22 of the specification shows that applicant has been successful in preparing retroviral vector stocks by transient transfection of 293T cells, used to infect HeLa-CD4+ cells and human U937 cells, and inserting the therapeutic gene or reporter gene RevM10 into the unique BamHI site of pTRIN. Briefly, the target cells were exposed to fresh retroviral stocks every 48 hours, and after the final transduction the transduced cells were infected with HIV-1. After 48-72 hours the cells were harvested and protein extracts prepared and assayed for the expression of the marker or therapeutic gene. Thus a retroviral particle capable of gene expression was obtained.

3. It is not readily apparent that one skilled in the art given applicant's disclosure alone, would be able to practice the invention over the scope claimed. In the instant situation, the claims embrace the method of using any retroviral vector for infection and transduction of any target cell, for HIV gene therapy. The specification gives specifics only for the retroviral vectors, target cells, and therapeutic genes and markers taught. It remains unclear that the state of the art regarding retroviral vectors at the time of filing was such that one skilled in the art would have been able to routinely isolate any retrovirus and any target cell for infection and transduction, and any therapeutic gene or marker for gene therapy in the treatment and prevention of retroviral

infections such as HIV, as broadly claimed. Such is considered to require an undue amount of experimentation in view of the lack of guidance provided in the specification as filed.

The specification is not enabling in its disclosure as it fails to teach the use of other retroviral vectors for gene therapy which could be utilized for the prevention or treatment of HIV. At the time of filing, gene therapy was proposed as a method of treating genetic disorders by replacing a defective gene with its normal counterpart, with the technical basis of gene therapy being gene delivery: the introduction of genes into the appropriate cells of the patient, based on retroviral vectors (Gilboa, et al 1994, see page 1, 1st para, and page 3, left col, 3rd para). It is unclear how other regulatory gene products besides Tat and Rev which activate HIV gene expression by binding to TAR and RRE to form response elements, would function in HIV, RNA based gene therapy strategy (Gilboa, et al, see page 1-2, right col, last para).

The specification is not enabling in its disclosure as it fails to teach how the TIN and TRAC retroviral vectors would be used for HIV gene therapy, or how many retroviral vectors would be utilized prophylactically or therapeutically, and whether or not the production of TIN and TRAC retroviral vectors would be more or less time consuming as outlined in the specification. " In addition, retroviral vectors are biological agents: they can only be made by living cells. As such, biological systems are not the easiest systems in the world to carry out good manufacturing practice (GMP) and quality assurance/quality control(QA/QC) (Anderson, 1998, see pages 25-27)". Hence, one cannot hasten the production of retroviral vectors including the TIN and TRAC vectors.

The specification is not enabling in its disclosure as it fails to identify how often the TIN or TRAC retroviral vectors would be administered to patients, or how the patients would be selected for HIV gene therapy. No mention is made of what pharmaceutically acceptable carriers the retroviral vectors would be administered, by what routes of retroviral vector administration, and whether or not immunosuppressants would be employed to modulate the immune response generated by the introduction of the TIN or TRAC retroviral vector particles due to repeat administration, or due to the newly expressed protein. "The immune system is designed to recognize and eliminate foreign gene products and cells which produce a foreign protein. The immune system is still likely to recognize a new or modified protein produced by the therapeutic gene, as a newly synthesized normal protein will appear abnormal to an immune system that has never been exposed to it (Anderson, see page 26, left col, 1st para)".

The specification is not enabling as it fails to address the specific target cells of this gene therapy, or how the cells would be selected and targeted by the retroviral vectors, or what *in vivo* tests would be conducted to ensure that efficient retroviral delivery had in fact occurred. No mention is made of whether the gene therapy would be exclusively *in vivo* or *ex vivo* or a combination of both, and what steps if any would have been taken to identify, isolate, and transduce cells with the appropriate therapeutic gene before readministration, if *ex vivo*. "Clinical protocols with retroviral vectors primarily use the *ex vivo* approach, where many of the target cells possess a high level of the natural MuLV amphotropic receptor, and are actively dividing at the time of exposure to the retroviral vector. The broad range of cells types

possessing the amphotropic receptor limits the target specificity utility of retroviral vectors *in vivo*. This is because retroviral vectors cannot be generated at a high titre, so it is not possible to get to the target cell type *in vivo* (Anderson, see page 25, right col, 1-3 para)".

The specification is not enabling in its disclosure as it fails to teach the therapeutic gene to be administered in the TIN and TRAC retroviral vectors, the size of the therapeutic gene, or which specific retroviral vector would be best suited with which therapeutic gene to maximize transduction efficiency.

"Transduction efficiency could be defined as the ability to reach all target cells with the therapeutic gene, and is dependent upon the target cell and the vector. Retroviral vectors have several characteristics which make them extremely appealing as vectors for gene therapy. Advantages include the ability to integrate their genome into the host cell chromosomes which allows the therapeutic gene to be maintained in the progeny for long term expression; they can transduce sequences up to 10 Kb thus allowing the transfer of large therapeutic genes; and they do not encode for viral proteins which have the potential of triggering an immune response toward the transduced cells. The retroviral vectors derived from oncoretroviruses such as murine leukemia virus, are the first vectors used in clinical trials, and are still the most popular vectors for gene therapy (G. Palu et al, 1999, see page 4, item 2)". No mention is made of specific promoters associated with the therapeutic gene which would ensure efficient expression. "The regulatory sequences which control gene expression do not remain active. In fact there is a tendency for the cells to recognize foreign promoters such as simian virus 40 (SV 40) and

cytomegalovirus (CMV) and inactivate them by methylation or other mechanisms (Anderson, see page 26, left col, 1st para)".

The specification is not enabling as it fails to teach whether the TIN and TRAC retroviral vectors would be utilized for other retroviral infections, apart from HIV. No mention is made of whether or not the TIN and TRAC retroviral vectors would be utilized in combination with other HIV gene therapy strategies, and what if any might these other therapies include.

4. The physiological art of utilizing retroviral mediated gene transfer to deliver therapeutic genes *in vitro* and *in vivo*, was well established and yielded excellent results as demonstrated by Cohli et al, 1994 and Crystal 1995, respectively. However, the method of utilizing a retroviral vector for gene therapy for the treatment or prevention of retrovirus infections such as HIV, at the time of the invention and prior to the invention, in an individual or human, would have been considered unpredictable.

5. In the absence of specific guidance which is lacking in the specification as filed, coupled with the reasons discussed above, it would require undue experimentation for one skilled in the art to practice the claimed methods or use the claimed products as disclosed in the specification.

The quantity of experimentation required to practice the invention as claimed would require the skilled artisan to identify other retroviral vectors which when combined with any therapeutic gene and the appropriate promoter, would result in the therapeutic gene being expressed in therapeutically effective amounts which would be utilized in gene therapy. One would have had to screen and characterize and render non-pathogenic, myriads of retroviral

vectors, capable of retroviral mediated gene transfer. The artisan would be left to attempt innumerable possibilities or combinations of retroviral vectors combined with therapeutic genes and promoters, administered by specific routes, in pharmaceutically acceptable carriers and administered in therapeutically effective amounts, to determine empirically whether or not gene therapy was indeed efficacious. Such is considered undue experimentation.

It requires undue experimentation to determine suitable response elements or functional equivalents such as a portion of RRE, or a mutated or manipulated version of RRE which would respond to Rev by maintaining the desired activity, which is to allow transport between the nucleus to cytoplasm.

It also requires undue experimentation for one skilled in the art to decipher transport factors originating from other viruses or host cells, analogous to Rev in that the transport factors would interact specifically with the response element to facilitate transport from the nucleus to the cytoplasm. The quantity of experimentation involved requires one to identify and isolate transport factors from any and all sources with the intended functional activity and specificity for binding. The artisan would be left to trial and error experimentation, not only to choose the appropriate sources of transport factors, but to choose as well suitable response elements from dauntless possibilities which would retain functional activity. Such is considered undue experimentation.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102 (b) as being anticipated by Yu et al, 1994.

Applicant claims a retroviral particle comprising a packagable RNA genome capable of being inserted into a target cell genome when in the form of a DNA provirus, said RNA genome carrying sequences which provide in the DNA provirus at least one selected gene capable of being expressed in the target cell and located within an intron in a transcription unit of the provirus, which transcription unit further comprises a polynucleotide response element responsive to a nucleus to cytoplasm transport factor.

Yu et al teaches a MMLV-based retroviral vector used to deliver RevM10 to human T cells. The RevM10 retains the Rev response element RRE binding and multimerizes with wild-type Rev and/or competitively inhibit RRE binding. Cloned human CEM cell lines stably expressing RevM10 were resistant to viral infection. Transduction of primary human PBLs with RevM10 vector conferred resistance to HIV-1 infection (Yu et al, 1994, see page 15, right col, 1st para). Yu et al also teaches that other groups have designed HIV-1 based retroviral vectors that are Tat-inducible (TIN) or that use heterologous promoter constructs (see page 20, right col, 2nd para).

Therefore, the claimed invention was anticipated by Yu et al who showed that a retroviral vector particle transduced with an expressed therapeutic gene conferred resistance in HIV infected cells, and as such would be used in retroviral infections, notably HIV gene therapy. Furthermore, the TIN vector utilized in the instant invention was anticipated by Yu et al.

Claims 1-4,10, and 14 are rejected under 35 U.S.C. 102 (b) as being anticipated by Cohli et al, 1994.

Applicant claims a retroviral particle comprising a packagable RNA genome capable of being inserted into a target cell genome when in the form of a DNA provirus, said RNA genome carrying sequences which provide in the DNA provirus at least one selected gene capable of being expressed in the target cell and located within an intron in a transcription unit of the provirus, which transcription unit further comprises a polynucleotide response element responsive to a nucleus to cytoplasm transport factor.

Cohli et al discloses retroviral vectors expressing chimeric RNAs containing the HIV-1 RRE and the HIV-1 packaging signal in sense and antisense orientations. The vectors were used to generate retroviral vector particles that were used to infect a human CD4+ lymphoid MT4 cell line. The HIV-1 packaging signal was required *in cis* for specific recognition and packaging of the viral genomic RNA; two copies of the HIV-1 genomic RNA were encapsidated per virus particle (see page 20, left col, 3rd para, and right col. 1st para).

Therefore, the claimed invention was anticipated by Cohli et al.

Claims 2-4. Applicant discloses the retroviral particle wherein the polynucleotide response element is responsive to a transactivation retroviral nucleus to cytoplasm transport vector such as HIV Rev, Rev response element (RRE) or a functional equivalent thereof.

Cohli et al teaches that RRE is a 234-nucleotide-long RNA sequence located within the env reading frame and forms a highly complex secondary structure containing a central stem I surrounded by stem-loops II, III, IV and V, where the stem-loop II has been found to contain the primary Rev-binding site which is also sufficient for Rev response in vivo. Cohli et al also discloses that the Rev-RRE interaction is sufficient to override the inhibitory action of the (CRS) or cis acting repressor such that the mRNAs can now reach the cytoplasm and become translated (see page 20, 2nd para).

Therefore the claimed invention was anticipated by Cohli et al who showed that the polynucleotide response element was in fact responsive to a transactivating retroviral nucleus to cytoplasm transport factor, since the Rev-RRE interaction allowed transport from the nucleus to the cytoplasm.

Claim 10. Applicant discloses a DNA construct encoding the packagable RNA genome for the retroviral vector particle operably linked to a promoter.

Cohli et al teaches that the retroviral vectors used in the study were derived from MoMuLV and the expression of the packaging signal-containing RNAs in these vectors, was under the control of the MoMuLV 5' LTR and HSV tk promoters (see page 22, last para).

Therefore, the claimed invention was anticipated by Cohli et al who showed that the retroviral vectors were linked to promoters.

Claim 14. Applicant discloses a retroviral particle production system comprising a set of nucleic acid sequences encoding the components of a retroviral vector particle.

Cohli et al teaches that retroviral vectors were first used to transfect an ecotropic packaging cell line Psi-2 and the vector particles released from this cell line were used to infect an amphotropic packaging cell line PA317. The resulting amphotropic pseudotyped retroviral vector particles were used to infect human CD4+ lymphoid cells lines, and G418 stable transformants selected (see page 22, right col, first 6 lines). Genomic RNA was isolated from the MT4 cells stably transformed with the retroviral vector particles (see page 21, left col, 1st para).

Therefore, the claimed invention was anticipated by Cohli et al who showed a retroviral particle production system capable of transduction and expression.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 5-11,15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Lisziewicz, 1992.

Applicant discloses a retroviral particle wherein the polynucleotide response element is responsive to a transactivating retroviral nucleus to cytoplasm transport factor such as HIV Rev or Rev response element (RRE) or a functional equivalent thereof.

Claim 2. Lisziewicz teaches that structural proteins expressed from these viruses are transported by a regulatory protein rev or rex which recognizes an RRE RNA element within the mRNA. The regulatory protein together with cellular factors transports RRE containing RNAs from the nucleus to the cytoplasm where the RNA is translated (see page 3, lines 27-32). Therefore, the claimed invention was anticipated by Lisziewicz who showed that transport from the nucleus to cytoplasm of the structural proteins was via the regulatory protein Rev.

Applicant discloses the retroviral particle wherein the polynucleotide response element is responsive to a transactivating retroviral nucleus to cytoplasm transport factor, which is the Rev response element RRE or a functional equivalent thereof.

Claims 2 & 4. Lisziewicz teaches that the retroviral vector is the vector of choice (see page 7, line 30), and the transfected vector integrates into the genome of the host cells where transcripts are produced in the cell containing RRE, which is then transported from the nucleus to the cytoplasm with the help of rev or rex thereby increasing the amount of packagable RNA and thus viral titer (see page 11, lines 11-20).

Applicant also discloses a DNA construct encoding the packagable RNA genome for the retroviral vector particle operably linked to a strong promoter such as the CMV promoter.

Claims 9 & 10. Lisziewicz teaches that the vectors include strong promoters such as long terminal repeat (LTR), CMV, TK, or SV40, where the preferred LTRs include the Moloney LTRs and HIV LTRs (see page 8, lines 1-4).

Applicant further discloses the retroviral particle wherein the selected gene is a therapeutic gene.

Claim 5. Lisziewicz teaches the choice of foreign genes to be inserted in the vector is dependent upon the effect sought, but could include for example beta-globulin, operably linked to the promoter (see page 8, lines 10-13 and 24-26, respectively).

Applicant discloses the retroviral vector particle where the packaging signal is contained within the intron in which the selected gene is located.

Claim 9. Lisziewicz also teaches that the RRE in the vector of the LTR can be inserted in front of the foreign gene or within an intron of the foreign gene(see page 9, lines 8-11).

Applicant discloses the use of a retroviral vector for gene therapy for infection or transduction of a target cell.

Claims 15-16. Finally, Lisziewicz teaches that retroviruses are being used with increased frequency as vectors to introduce foreign genes into eukaryotic cells, and the technique can be used to introduce genes into human somatic cells, and has application to human gene therapy. For example, retroviral vectors have been used to transduce hematopoietic cells that might be used for gene therapy of diseases affecting blood cells (see page 1, lines 9-11, and 15-22).

Therefore, the claimed invention was anticipated by Lisziewicz.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

February 10, 2000

JOHN LEGUYADER
PRIMARY EXAMINER
GROUP 1600